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Commentary and Reply to: Would smokers with schizophrenia benefit from a more flexible approach to smoking treatment?

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Would smokers with schizophrenia benefit from a more flexible approach to smoking treatment? [*Addiction*, 97 (2002), pp. 785–793]

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Commentaries

TREATING TOBACCO ADDICTION IN SCHIZOPHRENIA: WHERE DO WE GO FROM HERE?

The paper by McChargue *et al.* (2002) raises an important question regarding the treatment of tobacco addiction in schizophrenia—whether smoking abstinence or smoking reduction should be the ultimate goal. The authors discuss four published studies combining pharmacotherapy and psychosocial interventions for smoking cessation/reduction in schizophrenic smokers, and conclude that rates of smoking abstinence at trial end-point and 6-month follow-up assessment are much lower in these patients compared to the general population. Accordingly, they reason that smoking reduction might be a more realistic outcome for schizophrenics, especially since they may derive benefits from nicotine use for clinical and cognitive deficits associated with this disorder.

There are several important issues with respect to smoking reduction versus abstinence approaches for tobacco use in schizophrenia. First, harm reduction approaches have not been documented to decrease or eliminate the risk of developing smoking-related medical illnesses in either non-psychiatric or psychiatric smokers (Hughes 1998). This is important because schizophrenic patients seem to be at higher risk for developing cardiovascular disease and lung cancer compared to controls (Tsuang, Perkins & Simpson 1983; Lichterman *et al.* 2001). Secondly, while there seems to be growing evidence that many of the clinical and cognitive deficits in schizophrenia may be alleviated by nicotine/smoking (Adler *et al.* 1993; Dalack *et al.* 1998; George *et al.* 2002), and that nicotinic receptor function may be abnormal in the disorder (Freedman *et al.* 1997; Breese *et al.* 2000), one of the strongest environmental cues that promotes continued smoking is the act of smoking itself. As smoking cues promote smoking urges in schizophrenics (Tidey *et al.* 2001), it seems highly unlikely that long-term reductions in smoking behavior can be achieved in this population. Thirdly, an important variable that has emerged as a positive predictor of smoking reduction/cessation in this population is the use of clozapine (George *et al.* 1995; McEvoy *et al.* 1995) and other atypical antipsychotic agents. Atypical antipsychotic drugs have been shown to produce a sustained amelioration of sensory gating deficits associated with schizophrenia (Nagamoto *et al.* 1996; Light *et al.* 2000), and of negative symptoms and some neuropsychological deficits (Meltzer, Park & Kessler 1999), in contrast to nicotine, that produces transient effects on these outcomes due to nicotinic receptor desensitization (Leonard *et al.* 2000). Hence, these positive effects of medications for schizophrenia on smoking suggest that optimizing pharmacological treatments for schizophrenia with those for treatment of nicotine dependence (nicotine replacement, bupropion), in combination with modified behavioral treatments, may lead to enhanced smoking cessation outcomes, as observed in one study (George *et al.* 2000). In that study, long-term smoking abstinence in schizophrenics was linked to achievement of abstinence early in the treatment trial (George *et al.* 2000), as has been shown in treatment studies of non-psychiatric smokers. Fourthly, the fact that trial end-point smoking abstinence is not enduring at 6-month follow-up assessment is not surprising, as high attrition in smoking abstinence is also seen in studies with non-psychiatric smokers (Hughes *et al.* 1999). The extended use of available treatments (nicotine replacement, bupropion) combined with relapse–prevention therapy may enhance long-term cessation outcomes in schizophrenic smokers.

Thus, it seems premature to conclude that the goal of reducing smoking should be recommended for treating smoking in schizophrenia. However, smoking reduction as a transition to abstinence needs more careful evaluation in this population. More data are needed about the effects of reducing smoking on biomarkers associated with the development of smoking-related medical illness, as well as on whether reducing smoking (compared to not reducing) decreases their incidence. Development of nicotinic receptor agonists (not nicotine) that are safe for use in humans may also assist these patients in achieving long-term smoking abstinence, and remediate clinical and cognitive deficits that accompany schizophrenia. The authors are to be commended on their balanced discussion of this topic and for advocating that multiple smoking treatment strategies need to be evaluated in this population. The increasing interest by investigators, and the growing number of funded studies in this area, should greatly improve such treatment in the future.

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YES! SMOKERS WITH SCHIZOPHRENIA WILL BENEFIT FROM MORE FLEXIBLE TREATMENT APPROACHES

McChargue, Gulliver & Hitsman (2002) present a timely and insightful argument suggesting that individuals with schizophrenia might benefit from a more flexible approach to smoking treatment. Given the serious health consequences and weak efficacy of current treatments of tobacco smoking in this population (McChargue *et al.* 2002), new and more flexible approaches are warranted. More specifically, McChargue *et al.* suggest that the potential utility of reduction-focused approaches to tobacco treatment should be evaluated in schizophrenics because strong psychobiological factors undermine their quit attempts. The three reduction techniques suggested are: (1) limiting access to cigarettes, (2) reinforcing lowered smoking rates and (3) providing nicotine replacement. These suggestions are well justified in their article and may prove to be important steps towards a comprehensive approach to smoking risks in schizophrenics. The following comments are meant to support, extend and amplify these suggestions.

The high smoking-relapse rates, chaotic life-styles, limited cognitive and social resources and limited alternative reinforcers characteristic of schizophrenics make

it important to address systematically the duration and generalization of smoking treatment effects in these individuals. While McChargue *et al*. note briefly the generalization problem, specific methods to enhance generalization are not addressed in their important review. The failure of treatment effects to generalize across time and settings is common for all forms of drug and behavior therapy (Plaud & Eifert 1998) and is likely to be especially problematic with schizophrenics attempting to quit smoking. Generalization problems are associated with limiting access to cigarettes, the first of the three suggestions. While such access limitations may help reduce smoking rate and exposure to tobacco toxins in in-patient settings, in-patient limits are unlikely to promote long-term reductions in out-patient settings unless out-patient treatment also limits access or assures other environmental and/or pharmacological (NRTs or other) support. Thus, the long-term effectiveness of a limitations approach may require the involvement of family, social and out-patient resources, as undertaken in the case of some drug treatments and in the case of dialectical behavior therapy for the treatment of borderline disorders (Linehan 1993). Such a social–therapeutic system might use both restricted access to cigarettes and reinforcement procedures (McChargue *et al*.'s second suggestion) for smoking reduction or abstinence. However, given the limited resources of the health-delivery system, a comprehensive social–therapeutic system capable of restricting cigarette access effectively and providing reinforcement for lowered tobacco consumption will not be viable for many, if not most individuals with schizophrenia. This leads to the practical question of what economically feasible alternatives might be created for this population with strong motivations to smoke and minimal motivation to quit.

If individuals with schizophrenia find smoking to be highly reinforcing and have few alternative competing reinforcers, it may be desirable to develop new and relatively safe nicotine replacement therapies (NRTs) that are more reinforcing than current NRTs. The development of inexpensive, alternative nicotine replacement therapies that provide smoking-equivalent, phasic boluses of nicotine (or functionally equivalent, yet less dangerous drug) with fingertip control of nicotine timing and dose would almost certainly be of more reinforcement value than current NRTs. Of course, such NRTs would need to minimize toxic effects associated with tobacco cigarettes. Unlike currently available nicotine replacement therapies, cigarettes provide fingertip and immediate control over nicotine dose and sensory effects (Ashton, Stepney & Thompson 1979). Given the low economic status of most individuals with schizophrenia, NRTs will need to address the cost the NRT product, relative to the cost of relatively inexpensive tobacco cigarettes.

Finally, to the degree that individuals with schizophrenia are self-medicating schizophrenic symptoms and effects of long-term medication treatment, NRT will have to compete with smoking benefits over a protracted length of time if they are to provide sustained reductions in smoking rate and relapse. Thus, flexible approaches may need to include effective (rapid and substantial dose and finger-tip control) and less hazardous means of nicotine administration over prolonged periods of time.

In summary, the challenges of developing effective treatments for individuals with schizophrenia are at least as great as those outlined by McChargue *et al*. Their suggested smoking-reduction approach needs to be evaluated empirically and extended in a variety of directions. New and creative NRTs and pharmacological and psychosocial interventions are needed to compete with the high reinforcement value of smoking in schizophrenics. McChargue *et al*. are to be applauded for suggesting some initial steps that may prove useful in the march toward the reduction of smoking-induced harm in a group with few resources to counter the enticement of tobacco smoking. In addition, their neurobiological model of smoking reinforcement in schizophrenics incorporates many of the most current models of smoking motivation (Gilbert & Gilbert 1998; Hughes 1999) and recognizes the importance of a comprehensive model of intervention that incorporates individual differences in environment and personal vulnerabilities.

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RIGIDITY IN MEASURES OF SMOKING CESSATION

I and others before me (Henningfield 1994) believe that tobacco researchers have become overly rigid on insisting that long-term abstinence (LTA) is the gold standard for evaluating smoking cessation and interventions.

One major function of an treatment outcome is to detect efficacy. LTA is an insensitive measure to detect efficacy because it is a dichotomous outcome which poses a high hurdle. For example, if studies of antidepressants used 'the incidence of absence of any depressive symptoms over the last 6 months' as their major outcome many current treatments would have been deemed failures. This high hurdle is especially problematic when new treatments are studied. It is highly probable that early tests of a new treatment choose the wrong dose, etc. and produce a weak treatment effect that could be improved, yet these treatments are discarded because this weak effect is not detected by LTA.

LTA is also insensitive because it fails to measure other possible benefits of treatment. For example, policy interventions (US Department of Health and Human Services 2000) and cessation treatments (Hughes 2000) often decrease the number of cigarettes/day among non-abstaining adults. Recent findings suggest such reductions do improve health (Nordstrom *et al.* 2000). As another example, a smoker's longest period of previous abstinence is a powerful predictor of eventual cessation (Gilpin *et al.* 1997). Perhaps one effect of our treatments is to induce a longer period of abstinence which translates to eventual cessation months later.

Clearly, the smoking cessation field needs to begin to explore the relationship of these less ambitious, more sensitive measures with eventual LTA. If these measures were adequate proxies for LTA, this could greatly decrease the time and cost to screen new treatments or to improve the delivery of proven treatments.

Another function of an outcome measure is to indicate health benefit. One of the major rationales for LTA is that it is clear that LTA improves health (US Department of Health and Human Services 1990). However, given the strong dose–response relationship between smoking and mortality (US Department of Health and Human Services 1990), logically the best measure of health impact in a population should be the total exposure to tobacco toxins (Stratton *et al.* 2001). This could be indexed by total number of cigarettes smoked over a certain period. However, since reductions in cigarettes/day are likely to be accompanied by increases in intensity of smoking of the remaining cigarettes (Stratton *et al.* 2001), an alternative would be the average level of some biomarker of smoke intake over time (Stratton *et al.* 2001).

So why have tobacco researchers been so fixated on LTA? I think it is for three reasons: (l) LTA is thought to be verifiable and thus more scientific (although some disagree; Velicer *et al.* 1992); (2) non-LTA outcomes such are reduction in cigarettes/day are thought not to be maintained (although some disagree; Hughes 2000); and (3) LTA is thought to be a conservative outcome (although some argue overly conservative outcomes are problematic; Cohen 1994).

In summary, I would encourage authors of cessation studies to report several non-LTA as well as LTA outcomes and reviewers and editors to allow authors the space for these to be reported. Only then can we assess whether LTA is best conceived of as the gold standard or the 'gold wish' (Henningfield 1994).

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A REPLY TO THE COMMENTARIES ON SCHIZOPHRENIA AND SMOKING TREATMENT: MORE RESEARCH IS NEEDED

Our paper (McChargue, Gulluver & Hitsman 2002) explores whether patients with schizophrenia need to change smoking behavior at a slower rate and require greater reinforcement for change in order to compensate for any abnormal neurobiological factors that may undermine quit attempts. A review of the literature suggests that an alternative smoking treatment for people with schizophrenia draws upon a harm reduction model, which emphasizes skill acquisition and prompts abstinence once reduced exposure to tobacco toxins have been obtained and stabilized over time.

The commentaries echo the importance of the question about how to treat smokers with comorbid schizophrenia. The overall consensus is that consideration of alternative approaches is a valid direction to pursue. However, some caution should be taken when evaluating alterative approaches. The primary concern from the commentaries involves the role harm reduction should play in the treatment of smokers with schizophrenia. To clarify our position, we do not advocate that abstinence-based treatments be abandoned. Our hope is that future research will show more efficacious outcomes resulting from abstinence-based treatments. As George & Vessicchio (2002) suggest, newer and more innovative abstinence-based smoking treatments are being developed that target individuals with schizophrenia. For example, a recent study reports 50% short-term abstinence rates among smokers with schizophrenia who received 300 mg/day of bupropion SR in a placebo-controlled smoking treatment trial (George *et al.* 2002).

One issue that continues to plague smoking treatments for individuals with schizophrenia is the lack of data. For example, it is still unclear whether smokers with schizophrenia are capable of long-term abstinence. We concur with some of the commentators that future smoking treatments incorporate reports of long-term abstinence. However, we are not convinced that long-term abstinence, if achievable for this population, should be routed solely through traditional abstinence-based efforts. Nor are we convinced that harm reduction should be the ultimate goal for this subgroup of smokers. At the very least, we suggest that harm reduction techniques be used as a transitional step to abstinence.

To date, harm reduction approaches applied to smokers with schizophrenia remain more conceptual than empirical. The commentaries address many important issues for researchers to consider when evaluating these approaches. First, more data are needed showing that smoking reduction corresponds with reduced biomarkers (George & Vessicchio 2002). In fact, we agree with Hughes (2002) that reduced biomarkers may be a more appropriate measure of harm reduction effects rather than the number of cigarettes smoked per day. Secondly, the evaluation of treatment duration and generalization should also be considered (Gilbert 2002). As Gilbert discusses, in-patient populations are very different from out-patient populations. Harm-reduction techniques are easier to implement in in-patient settings. In contrast, out-patient smokers have different social and environmental influences that may hinder or help harm reduction efforts. Given the inherent differences between in-patients and out-patients, we concur that treatment approaches should be tailored. Thirdly, the use of nicotine replacement therapies (NRT) has been the most widely espoused technique for harm reduction. Many suggest that NRTs be administered for long periods of time and at higher doses. Nevertheless, we concur with Gilbert (2002) in that, if NRTs are considered, researchers should assess the accrued monetary cost of such interventions.

In conclusion, many unanswered questions remain. Our hope is that this 'for debate' series will start a dialog about how to address extremely difficult to treat underrepresented smoking populations. As reflected in many of the commentaries as well as the original paper, much research is needed to adequately evaluate smoking treatment for individuals with schizophrenia. The extent to which harm reduction approaches represent a viable alternative remains to be seen.

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